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Endogenous doesn't always mean innocuous: a scoping review of iron toxicity by inhalation

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Abstract

Ambient air pollution is a leading risk factor for the global burden of disease. One possible pathway of particulate matter (PM)-induced toxicity is through iron (Fe), the most abundant metal in the atmosphere. The aim of the review was to consider the complexity of Fe-mediated toxicity following inhalation exposure focusing on the chemical and surface reactivity of Fe as a transition metal and possible pathways of toxicity via reactive oxygen species (ROS) generation as well as considerations of size, morphology, and source of PM. A broad term search of 4 databases identified 2189 journal articles and reports examining exposure to Fe via inhalation in the past 10 years. These were sequentially analyzed by title, abstract and full-text to identify 87 articles publishing results on the toxicity of Fe-containing PM by inhalation or instillation to the respiratory system. The remaining 87 papers were examined to summarize research dealing with *in vitro, in vivo* and epidemiological studies involving PM containing Fe or iron oxide following inhalation or instillation. The major findings from these investigations are summarized and tabulated. Epidemiological studies showed that exposure to Fe oxide is correlated with an increased incidence of cancer, cardiovascular diseases, and several respiratory diseases. Iron PM was found to induce inflammatory effects *in vitro* and *in vivo* and to translocate to remote locations including the brain following inhalation. A potential pathway for the PM-containing Fe-mediated toxicity by inhalation is via the generation of ROS which leads to lipid peroxidation and DNA and protein oxidation. Our recommendations include an expansion of epidemiological, *in vivo* and *in vitro* studies, integrating research improvements outlined in this review, such as the method of particle preparation, cell line type, and animal model, to enhance our understanding of the complex biological interactions of these particles.

Keywords

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Competing Financial Interests

The authors declare they have no actual or potential competing financial interests.

Abstract

BACKGROUND: Ambient air pollution is a leading risk factor for the global burden of disease. One possible pathway of PM toxicity is through iron, the most abundant metal in the atmosphere.

OBJECTIVES: This paper will consider the complexity of iron toxicity by inhalation focusing on the chemical and surface reactivity of iron as a transition metal and possible pathways of toxicity via reactive oxygen species generation as well as considerations of size, morphology and source of PM.

METHODS: A broad term search of 4 databases identified 2189 journal articles and reports examining iron by inhalation in the past ten years.

RESULTS: These were sequentially analysed by title, abstract and full-text to identify 87 articles publishing results on the toxicity of iron containing particulate matter by inhalation or instillation to the respiratory system. The remaining 87 papers were examined to summarise research dealing with *in vitro*, *in vivo* and epidemiological studies involving iron PM or iron oxide by inhalation or instillation. The major findings from these papers are summarized and tabulated.

DISCUSSION: Epidemiological studies have shown that exposure to iron oxide is correlated with increased incidence of cancer, cardiovascular disease and several respiratory diseases. Iron PM has been shown to induce inflammatory effects *in vitro* and *in vivo* and is able to translocate to remote locations including the brain following inhalation. A likely pathway for the toxicity of iron containing PM by inhalation is via the generation of reactive oxygen species which can lead to lipid peroxidation and DNA and protein oxidation. Our recommendations include an expansion of epidemiological, *in vivo* and *in vitro* studies, integrating research improvements outlined in this review, such as method of particle preparation, cell line type, and animal model, to solidify our understanding of the complex biological interactions of these particles.

Introduction

The World Health Organisation estimates that 4.2 million deaths occur every year as a result of ambient air pollution exposure via chronic obstructive pulmonary disease, lung cancer, heart disease, stroke or acute respiratory infections, with an additional 3.8 million deaths attributed to exposure to household smoke and fuels (WHO 2018). Suspended PM is classified by aerodynamic size in micrometres (μm) and measured by mass as milligrams per cubic metre. The terms PM_{10} and $PM_{2.5}$ generally describe airborne PM with an aerodynamic diameter of less than 10 μm or 2.5 μm respectively (see **Figure 1**). Fine particles with an aerodynamic diameter of less than 2.5 μm exhibit different properties to larger particles in terms of origin, composition, lung penetration, toxicity and immunogenicity and different morphogenic characteristics in terms of surface area, surface reactivity, and porosity (Achilleos et al. 2017; Chow and Watson 1998; Xing et al. 2016). Similarly, ultrafine particles ($PM_{0.1}$ <0.1 μm aerodynamic diameter) exhibit particular properties and characteristics compared to coarse or fine particles. Ultra-fine particles (UFPs) are more likely to be deposited in the alveolar region of the lung and are able to translocate through the epithelium (Bräuner et al. 2007). Nanoparticles (NPs) are also classified as particles <0.1 μm in diameter

however these particles can be distinguished as NPs are deliberately synthesized for commercial use whereas UFPs are by-products of combustion or other anthropogenic sources (see **Figure 1**).

Particulate air pollution has been specifically associated with adverse cardiovascular events including myocardial infarction, hypertension, congestive heart failure, coronary heart disease and stroke (Ebert et al. 2012; Laden et al. 2006; Stone et al. 2017). Both epidemiological and toxicological studies into cardiovascular effects of coarse and fine PM are summarized in a recent review (An et al. 2018). PM has been associated with an increase in emergency room visits and hospitalisations in paediatric asthmatics (Pollitt et al. 2016) as well as a reduction in pulmonary function (S Wu et al. 2013). Ambient exposures to $PM_{2.5}$ have also been associated with increases in lung cancer mortality, where for each 10 $\mu g/m^3$ increase in $PM_{2.5}$ there was a 15-27% increase in lung cancer mortality (Turner et al. 2011). Subsequently, the International Agency for Research on Cancer (IARC) classified outdoor air pollution and PM as carcinogenic to humans (Group 1) in October 2013 (IARC 2013). Children, the elderly and the chronically ill appear to be particularly vulnerable to the adverse effects of PM (Babadjouni et al. 2017; Cakmak et al. 2009; Valavanidis et al. 2008).

[Figure 1]

The toxicity of PM is complex due to a multitude of factors. The surface area of airborne particles varies inversely with aerodynamic diameter (Oberdorster et al. 1996). Particle size also determines deposition within the respiratory tract and the potential health impacts (Chow and Watson 1998). The abundance and availability of surface reactive sites can also modulate reactivity with human cells and tissues (Oberdorster et al. 1996). Variation in health outcomes from PM inhalation are dependent not only on size and morphology but also on the type of components present in the PM (Achilleos et al. 2017; Chen et al. 2013; Wu et al. 2011). Studies undertaken by Diociaiuti et al. (2001) and Sandstrom and Forsberg (2008) support this proposition, reporting results more consistent with variations in composition than size. Schwarze et al. (2006) suggest that current air-quality standards based on the estimated mass of suspended particles may ignore the effect particle composition has on toxicity. Notwithstanding the accepted use of size fractionated risk assessment of airborne PM, the available literature suggests that physicochemical characterisation of particles is at least an equally important predictor of toxicity and reactivity compared to size.

Iron is the most abundant metal in the atmosphere (Ault et al. 2012; Beck-Speier et al. 2009). Atmospheric iron comes from a variety of sources: brakes and abrasion of train rails (Moreno et al. 2017; Wang et al. 2016); vehicle exhaust as iron scraps from piston motion (Li et al. 2017; Liati et al. 2013); coal and oil fly ash (Lu et al. 2009; Silva et al. 2009); mining activities such as drilling, blasting, collection and transportation (Tavares et al. 2014); fumes associated with welding (Falcone et al. 2018b); steel production particularly the formation of EAF-dust from electric arc furnace recycling of scrap iron (Wu et al. 2014); waste incineration (Yu et al. 2013); and naturally occurring geogenic dusts (DeWitt et al. 2017; Pritchard et al. 1996).

Concentrations of iron in the atmosphere vary significantly, largely due to particle source. For example in air pollution in Switzerland the iron concentration ranged from 0.07 – 1.4 $\mu g/m^3$ (Bukowiecki et al. 2005), however, much higher concentrations have been identified in mineral dusts in the Middle East, 0.42 – 2.85 $\mu g/m^3$ (Engelbrecht et al. 2009) and in subway stations, 2.67 – 47.88 $\mu g/m^3$ (Wang et al. 2016). Source also has an impact on chemical composition. Iron-rich particles in

the atmosphere are commonly found to be additionally associated with other elements including other transition metals, aluminium, silica, potassium, sulfur and other organic particles (Ault et al. 2012, Li et al. 2017, Sanderson et al. 2016, Tavares et al. 2014). Li et al. (2017) analysed the PM in Shanghai, China in late 2016 and found iron present in both the coarse (>1 μm) and fine (<1 μm) fractions. This iron was commonly associated with the presence of oxygen, often in the form of hematite (α-Fe_2O_3) and magnetite (Fe_3O_4) oxides. In all cases it is important to consider that the iron containing PM is often associated with additional components which increases the complexity of any potential toxicity.

Iron has long been considered one of the more biologically innocuous heavy metals, in part due to its high concentration in the human body and its central role in human physiology. As such, it is has often been ignored in studies examining the toxicology of PM. However, transition metal content and iron mobilization have both been associated with the adverse health effects of PM (Wu et al. 2018). Poorly-liganded iron has been implicated in a number of neurological diseases including Parkinson's, Huntington's, and Alzheimer's diseases (Kell 2010). Genetic hemochromatosis patients, who have an overload of iron, suffer complications involving hepatic failure from cirrhosis or hepatocellular carcinoma with rates 93-240 times that of age-matched controls (Toyokuni 2002, 2009). A possible pathway to injury is the production of reactive oxygen species when transition metals, such as iron, are present, which leads to inflammation and subsequent injury (Funke et al. 2013; S Wu et al. 2013). Due to the inherent risks associated with this humans have extensive pathways for dealing with free iron (Dev and Babitt 2017) however, when these pathways are overwhelmed via excessive exposure or genetic variability between individuals, this may lead to injury or illness.

This paper will consider the complexity of iron toxicity by inhalation exposure focusing on the chemical and surface reactivity of iron as a transition metal, possible pathways of toxicity via reactive oxygen species, considerations of size and morphology, and health outcomes associated with iron from different sources, including occupational sources. Conclusions drawn from epidemiological, *in vivo* and *in vitro* studies from the past 10 years will be summarized, with the latest research on nanomaterials used to inform toxicity data on UFPs.

Methods

A detailed search of available literature from the past 10 years on iron oxide containing PM was conducted on 03 April 2019. The databases employed were ProQuest, Scopus, Web of Science and PubMed. The literature search was left deliberately broad to ensure all results were captured. Three separate searches were used. The search strategy employed for all databases was as follows:

1. particulate matter AND iron oxide AND (2009/01/01 to present)
2. 'iron oxide' AND (inhalation OR inhale) AND (2009/01/01 to present)
3. iron AND (in vivo OR in vitro OR epidemiolog*) AND (inhalation OR inhale OR instillation OR instill) AND (2009/01/01 to present)

Results were limited to reports and journal articles written in English.

Results

Results from the three searches outlined above were pooled. This database search identified 2189 papers, with an additional 23 papers located from other sources. Once duplicates were removed this left 1276 results (**Figure 2**). These articles were screened by title and 678 records which were irrelevant to the topic or were dealing with non-atmospheric forms of iron containing PM were removed. A further 467 were removed following a screening of abstracts using the same exclusion criteria outlined above. The full-text of the remaining 131 were reviewed and 44 additional papers were removed. Only papers describing raw data dealing with *in vivo*, *in vitro* or epidemiological data following instillation/inhalation of iron containing PM were included. Reviews were removed. General PM papers were only included if they provided specific data on the iron component. The remaining 87 papers were included in the review. These articles are marked in the reference list with an * and the major findings from each paper are summarized in **Tables SM1 – SM5** in the **Supplementary Material**.

[Figure 2]

Discussion

Uptake and fate of PM following inhalation

The first hurdle when considering toxicity by inhalation is determining the biological fate of PM following entry into the respiratory system. The region of the respiratory system where PM is most likely to deposit is largely dependent on breathing pattern (Brown et al. 2008) and particle size, with coarse particles (PM_{10}) more likely to deposit in the upper nasopharygeal region and UFPs ($PM_{0.1}$) more likely to deposit in the lower pulmonary region (see **Figure 3**) (Chow and Watson 1998).

[Figure 3]

The second consideration is twofold. Firstly, once in the lung, are the particles incorporated into cells and are they able to induce a biological response that will lead to significant adverse health, such as severe inflammation? And secondly, are the particles able to translocate from the lung into the blood stream and potentially to other organs to cause secondary effects?

Mechanisms of incorporation from the lung into the body include dissolution, translocation into epithelial cells and interstitial tissue, migration of particles caused by mucociliary motion, and migration caused by incorporation into alveolar macrophages (see **Figure 4**). Non-biosoluble particles deposited in the lungs are cleared by mucociliary transport moving particles from the nasal passage and trachea-bronchiolar region to the oropharynx, where they are swallowed (ECETOC 2013) or recognized by alveolar macrophages (AM) and engulfed (Kunzmann et al. 2011). Studies involving titanium oxide (TiO_2) particles have shown that following inhalational deposition deep in the rat lung, particles were able to translocate to the tracheobronchial and mediastinal lymph nodes (Morfeld et al. 2012, Warheit et al. 1997). However, this has not been analysed for iron oxide containing particles and the single study investigating carbonyl iron, found translocation to the

tracheobronchial lymph nodes only in cases of inhalation of extremely high concentrations (250 mg/m^3) (Warheit et al. 1997).

In vitro studies involving iron NPs have been shown to be incorporated into a variety of cell types, likely via phagocytosis or pinocytosis, leading to the formation of NP containing membrane-bound vesicles (see **Figure 4**) (Guo et al. 2009; Könczöl et al. 2011; Lee et al. 2014; Liu et al. 2012; Zhu et al. 2011). Following incorporation of these particles, physical changes to the cell that have been observed include: mitochondrial swelling and disappearance of the mitochondria (Zhu et al. 2011) as well as the disappearance of other organelles (Park et al. 2014a); changes in cellular morphology (Dwivedi et al. 2014); and separation of cells producing intercellular gaps (Apopa et al. 2009). Changes to cytosolic organelles and increased gene transcription suggest that cell death in some cell lines may be driven by autophagy via oxidative pathway, ferroptosis, and not apoptosis (Park et al. 2014b).

Following cellular uptake, iron oxide NPs are found in endosomes or lysosomes. Once inside lysosomes, enzymes act to decompose these particles releasing iron into the total labile iron pool (Liu et al. 2013). Additionally, the acidic pH (4.5-5.0) inside the lysosome can lead to increased solubilisation of iron and potential chemical conversion of iron oxide into a more redox active form (see **Figure 4**) (Guo et al. 2009).

Under normal physiological conditions levels of unliganded iron are very low. Iron in both ferrous and ferric forms is highly reactive and kept bound to proteins or chelated to avoid generation of reactive oxygen species (ROS) (see **Chemistry of Iron** section). However, unlike the digestive system, the lung does not have specific pathways for receiving large quantities of iron, with a focus on sequestering the metal into a less reactive state mostly through storage in ferritin (Ghio et al. 2009). Alveolar macrophages (AMs) are important mediators of iron homeostasis by controlling cellular iron import and storage, with AMs being a major pathway for iron clearance from the lung (Allden et al. 2019, Philippot et al. 2014). In line with this, expression of membrane bound proteins such as CD71, which is responsible for the uptake of iron-bound complex diferric transferrin, appear altered in patients with progressive fibrotic lung disease (Allden et al. 2019). While critical to a complete understanding of iron within the body, homeostasis and control of iron stores are outside the scope of this review. For additional information see recent reviews by Ganz and Nemeth (2015) and Sukhbaatar and Weichhart (2018).

An *in vivo* study in man examined the response to iron particles where an instilled dose of synthesized Fe_2O_3 induced a transient acute inflammatory response (Lay et al. 1999). The dose used in this study was equivalent to breathing heavily polluted urban air for 24 to 48 hours. The authors selected this particle due to its low reactivity and were surprised by the extent of the inflammatory response. Subsequent studies have identified significant increases in bronchoalveolar lavage fluid (BALF) cells, particularly neutrophils and alveolar macrophages across a range of human, mouse and rat models (see **Table SM3** and **Table SM4** in the **Supplementary Material**) (Beck-Speier et al. 2009; Park et al. 2015; Srinivas et al. 2012; Sutunkova et al. 2016). An up to 20-fold increase in cytokines associated with inflammatory response has been observed following both inhalation and instillation of iron particles *in vivo* (Park et al. 2010; Park et al. 2015; Srinivas et al. 2012), particularly IL-12, IgM and IgG as well as IL-6, IL-4 and IL-5. Additionally, Park et al. (2010) found a significant increase in IgE in blood but not BALF which is important as most studies focus on BALF analysis.

[Figure 4]

In addition to their ability to induce transient acute inflammation, UFPs are also able to translocate outside the lung with clearance and retention controlled by interstitilization rather than macrophage mediated clearance, with rapid translocation to endothelial and interstitial sites, then onto lymphatic channels and the blood (ECETOC 2013). Iron particles instilled in rats have been shown to pass through the alveolar-capillary barrier and into the systemic circulation less than 10 minutes after instillation and have an extremely long elimination half-life (22.8 days) (Zhu et al. 2009). NPs have been located (via TEM) in the olfactory region of the brain of rats following inhalation suggesting possible translocation from the nasal cavity along the olfactory nerve fibres (see **Figure 4**) (Hopkins et al. 2018; Sutunkova et al. 2016). Near edge X-ray absorption fine structure (XANES) measurements have also determined that Fe^{3+} levels were significantly increased in the olfactory bulb and brain stem following instillation in mice (Wang et al. 2011) as well as the cortex, hippocampus and midbrain (Wang et al. 2011; J Wu et al. 2013). Instilled and inhaled iron has also been found in organs rich in mononuclear phagocytes including the liver, spleen, kidney and testicles (Zhu et al. 2009).

A large number of studies determining inhalational toxicity use instillation as a dose delivery method. This is problematic as: instillation bypasses the upper respiratory tract and is unlikely to reach the lower alveolar regions; it results in high exposure concentrations which are physically isolated leading to uneven exposure; these high concentrations are likely to overwhelm clearance mechanisms in sensitive models; and particles suspended in solution are unlikely to have surface chemistry and agglomeration properties similar to those in the aerosol (ECETOC 2013). Therefore care needs to be taken when considering these results, particularly in cases where comparative inhalational studies are not available.

It is important to note that rats and mice have been used for the vast majority of *in vivo* PM studies, however, there is a different distribution of inhaled particles in the rat and the human lung (ECETOC 2013) due to variances based on function, with rodents being nose-only breathers and humans breathing through both nose and mouth, as well as structural variations (Brown et al. 2008). Additionally, significant differences have been found between the particle clearance rates in small mammalian models (mice and rats) and larger models (canines and humans) with much slower clearance seen in the larger species (Kreyling et al. 2006) (implications of lung overload in rats are discussed in detail in the **Challenges of Research** section below). Long term clearance of particles from the alveolar region of the lung varies significantly with rats having a retention half-time of 60-80 days but up to two years in humans (Brown et al. 2008).

Chemistry of Iron

Iron present as a component of PM is usually in the Fe^{2+} or Fe^{3+} form, often as oxides (FeO, Fe_2O_3 or Fe_3O_4), particularly when obtained from combustion or mineral sources. While pure iron and other iron salts, including carbonate, sulfate and chloride, may be in PM they are usually present in much lower concentrations. It should be noted that in PM these iron oxides are not usually in isolation but are associated with other oxides, metals and carbon (Engelbrecht et al. 2009, Li et al. 2017, Tavares et al. 2017).

As a highly reactive transition metal iron can initiate Fenton-like reactions (equation 2 **Figure 5**) which generate reactive oxygen species (ROS) which can, in turn, promote localized adverse health effects (Beck-Speier et al. 2009). The hydroxyl radical, which is produced via this reaction, is extremely reactive, with a half-life of about one nanosecond (Kehrer 2000). Pathways of ROS damage via the hydroxyl radical include DNA oxidation and subsequent damage of both bases and the deoxyribose backbone leading to the potential for increases in cancer; lipid peroxidation, which involves the reaction of free radicals with the fatty acids in the cell membrane, leading to membrane disruption and potentially ferroptosis; and protein damage via protein oxidation (Kehrer 2000; Valko et al. 2007) (see **Figure 5**).

[Figure 5]

The majority of papers showing iron particle induced cytotoxicity suggest that iron controlled generation of ROS is the major pathway of toxicity with a significant increase in ROS seen in numerous *in vitro* studies (Bhattacharya et al. 2012; Könczöl et al. 2011; Park et al. 2014a; Park et al. 2014b; Rajiv et al. 2016; Zhu et al. 2011). Increase in ROS production has also been shown following *in vivo* exposure to Fe_3O_4 (Dwivedi et al. 2014; Könczöl et al. 2013; J Wu et al. 2013) and Fe_2O_3 (Zhu et al. 2011). Interestingly, some papers which failed to show a significant increase in ROS when exposed to iron particles alone, did show a significant increase in ROS when exposed to iron particles in the presence of a co-oxidant such as hydrogen peroxide (Guichard et al. 2012), carbon black (Berg et al. 2010; Guo et al. 2009), ascorbic acid (Bhattacharya et al. 2009) or quinones (Lyngsie et al. 2018; Valavanidis et al. 2008) suggesting that redox cycling might play an important part in this process.

Further evidence of the potential for a redox cycling pathway of toxicity can be seen in *in vitro* studies showing evidence of cellular incorporation of both carbon black and iron oxide with co-localisation in endosomal-like or lysosomal-like structures (Berg et al. 2010). Carbon black can reduce Fe^{3+} to Fe^{2+} which is membrane permeable and can undergo further intracellular redox reactions in the cytosol leading to the generation of ROS (Berg et al. 2010). Carbon black and Fe_2O_3 co-incubated with H_2SO_4, to replicate lysosomal conditions, produced both Fe^{2+} and Fe^{3+} suggesting redox cycling in lysosomes is possible (Guo et al. 2009). Supporting this there was an increase in generation of ROS *in vitro* following exposure to Fe_2O_3 in the presence of carbon black. Interestingly, this increase was not concentration dependent for either particle, suggesting that the ratio between the iron oxide and the carbon black may be of importance (Berg et al. 2010; Guo et al. 2009). Low levels of cytotoxicity were seen in this study, which could be reduced by surface oxidising the carbon black, suggesting that the redox cycling between these particles was responsible for the toxicity (Berg et al. 2010). Significant protein oxidation was seen for Fe_2O_3 in the presence of carbon black as well as lipid peroxidation when both particles were in combination but not for either particle alone (Guo et al. 2009). This effect was also seen with iron oxide in the presence of soot particles which caused a significant increase in oxidized glutathione, indicative of oxidative stress (Zhong et al. 2010).

In humans there are several factors opposing the iron-induced ROS damage pathway, including the low biosolubility of iron and the sequestering of free iron by binding proteins (Beck-Speier et al. 2009). Under normal biological conditions iron is stored as an iron-ferritin complex, however, under pathological conditions associated with the production of ROS, e.g. cancer and atherosclerosis, iron

can be released. Free iron can be reduced to Fe^{2+} and then participate in the Fenton reaction to produce the hydroxyl radical (Singh et al. 2010). An *in vitro* study showed that iron oxide NPs (Fe_2O_3) caused an increase in endothelial cell permeability, mediated via ROS-modulated microtubule remodelling leading to the formation of intercellular gaps (Apopa et al. 2009). This permeability increased within 10 minutes of exposure to NPs and persisted for up to 5 hours after exposure ceased (Apopa et al. 2009).

Formation of ROS requires the aerosol fraction of iron to be soluble (Longo et al. 2016), thus we need to determine if iron can become bioavailable following inhalation. This is related both to the deposition and translocation described earlier as well as the solubility of the iron within the PM. Iron solubility has significant variability relating to iron source (Pritchard et al. 1996). Fu et al. (2012) analysed the total soluble fraction of iron from a range of sources and found that under low pH conditions in the presence of light, mineral dust had a total iron content of 3.1%, 4.5% of which was soluble iron, whereas fly ash from an oil burning plant contained 9.3% iron, 85.9% of which was soluble. There were also significant differences when comparing industry to natural dusts with iron sourced from industry-derived PM being ~4% soluble compared with mineral PM ~0.4% soluble (Ault et al. 2012; Fu et al. 2012). It has been noted that in mineral dusts the solubility of iron is inversely proportional to the total iron content (Longo et al. 2016). Interestingly, the type of soluble iron present also varied by source with iron from biomass burning present mainly as ferrous iron (Fe^{2+}) where total dissolved iron from fly ash and mineral dust was present mostly as ferric iron (Fe^{3+}) (Fu et al. 2012).

Additionally, solubility of iron in the aerosol has been shown to increase with estimated travel time from the source, which is likely linked to an associated decrease in pH with travel time (Longo et al. 2016). Despite the fact that Fe^{2+} is more soluble than Fe^{3+} no correlation was seen between oxidation state and solubility in a study by Longo et al. (2016). Solubility also varied by concentration with lower concentrations producing more soluble iron (by %) resulting in no clear concentration-dependent toxicity (Zhu et al. 2011). Additionally, Fe_2O_3 particles showed moderate solubility in alveolar macrophages despite being insoluble in extracellular media suggesting composition of the media used to deliver the particles can alter solubility and therefore also potentially toxicity (Beck-Speier et al. 2009). The temperature at which the iron oxide particles are created can also have a marked effect on the solubility of the iron, particles created at a lower temperature (250^{o}C) have been shown to have a water-soluble iron content 23 fold higher than those produced at a higher temperature (800^{o}C) (Lay et al. 2001). The fact that PM solubility could be controlled by particle size, morphology, composition, oxidation state of iron, or particle ageing processes in aerosols such as photoreduction or organic ligand association (Longo et al. 2016) or a combination of these factors, exacerbates the complications seen with aerosol iron chemistry.

Following phagocytosis particles can be dissolved in lysosomes, due to a lower pH, generating free iron ions which can subsequently be involved in generating ROS (Zhu et al. 2011). Solubility of both Fe^{2+} and Fe^{3+} has been shown to increase with increasing acid strength and epithelial cells exposed to Fe_3O_4 particles saw a decrease in cell viability and an increase in interleukin production when acid or secondary organic aerosol or both were added along with the particles (Baber et al. 2011; Ghio et al. 2009). We know that iron becomes bioavailable following inhalation as studies have shown a significant increase in ferritin expression following inhalation in rats indicating an increase in

bioavailable iron (Zhong et al. 2010; Zhou et al. 2003).

Biological Effects of Iron

Cytotoxicity and Genotoxicity

Cytotoxicity of iron NPs varies greatly between studies and care needs to be taken when drawing conclusions from single studies as different cell lines, particle exposure time, types of particles and even method of preparation of particles show significant variation in their induced level of cytotoxicity (see **Table SM1** of **Supplementary Material** for a summary of iron oxide particle *in vitro* studies). Fe_2O_3 NPs caused a significant decrease in metabolic activity (MTT assay) from 3.75 μg/ml in MSTO cells but tolerated 30 μg/ml in the slower proliferating 3T3 cells in the same study suggesting significant variation in cell types used in *in vitro* studies (Brunner et al. 2006). Some studies have concluded that iron particles produced no cytotoxic effects or were cytotoxic only at extremely high concentrations (Freyria et al. 2012; Szalay et al. 2012; Williams and Zosky 2019); where other studies have shown moderate decreases in cell viability (20-30% at 50-200 μg/ml) (Könczöl et al. 2011; Rajiv et al. 2016); and further studies have shown substantial decreases in cell viability (70-90% at 50-100 μg/ml) (Dwivedi et al. 2014; Park et al. 2014a; Zhu et al. 2011).

Overall no clear conclusions can be drawn from these studies due to the significant variation between methods although it can be seen that monkey kidney cell lines seem to show lower cytotoxicity than human epithelial cell lines or alveolar macrophages. Additionally, flame synthesized particles appear to produce a higher cytotoxicity than purchased NPs, suggesting that surface oxidation or morphology may be important. Direct examination of freshly prepared flame synthesized, chemically synthesized and purchased NPs would be a useful future study to allow for direct comparison of these particles.

Genotoxic effects have also shown significant variation between studies. Iron particles have been shown to produce significant DNA damage ($p \leq 0.001$) at concentrations as low as 10 $\mu g/cm^2$ (Bhattacharya et al. 2009). With Fe_3O_4 NPs showing significant oxidative DNA damage compared to control (Karlsson et al. 2009; Totsuka et al. 2014) and Fe_3O_4 NPs and bulk particles producing genotoxic effects (via DNA migration) in epithelial cells that were partially inhibited by ROS scavengers (Könczöl et al. 2011).

Pulmonary Effects

A significant increase in lactate dehydrogenase (LDH) was seen in a number of studies indicating cellular injury (Demokritou et al. 2010; Park et al. 2015; Zhong et al. 2010) as well as an increase in total protein indicating altered vascular permeability (Srinivas et al. 2012). A 2.0 mg/kg dose of iron oxide NPs in mice showed a six fold increase in apoptotic cells (Park et al. 2010; Park et al. 2015) with increasing intracellular iron concentrations shown to promote ferroptosis, a nonapoptotic form of cell death characterized by reduced mitochondrial size with increased membrane density which is believed to occur via the iron-mediated accumulation of lipid peroxidation (Manz et al. 2016).

Alveolar wall thickening indicating potential fibrosis (Zhu et al. 2008) and dose dependent weak pulmonary fibrosis and interstitial inflammation (Szalay et al. 2012) are just some of the structural changes observed in *in vivo* models following instillation of iron particles. Mice exposed to long term

Fe_3O_4 NPs showed a significant increase in alveolar wall thickness, peribronchiolar wall thickness, perivascular wall thickness and interstitial lung inflammation (Presume et al. 2016; Teeguarden et al. 2014). Additionally, following iron particle instillation, rats decreased their total body weight with significant decrease in lung weight (Szalay et al. 2012).

Increased iron levels have also been correlated with several types of cancer with cellular redox imbalance found in various cancer cells (Valko et al. 2007). Iron dysregulation has been associated with mutagenesis and enhanced tumour growth (Manz et al. 2016). Long term exposure (10 weeks) to low dose nano Fe_2O_3 resulted in neoplastic-like transformation of human small airway epithelial cells likely via an ROS pathway involving altered iron homeostasis (Stueckle et al. 2017).

Iron dysregulation is also a feature of chronic obstructive pulmonary disease (COPD) (Cloonan et al. 2017) with serum iron and ferritin increased in smoking patients with COPD compared with healthy non-smokers. There were also significant increases seen for both iron and ferritin in lavage fluid (Ghio et al. 2008) with increased rates of COPD among ferrous metallurgy workers which maintained significance when adjusting for age and smoking status (Bala and Tabaku 2010). **Figure 6** shows a side-by-side comparison of the locations of steel processing plants (**Figure 6a**) and iron ore mining locations (**Figure 6c**) in the UK compared with relative risk of COPD mortality by local authority district 2008-2012 (**Figure 6b**). As can be seen from this graphic there is a high correlation between areas with significant iron ore mining and processing and the risk of COPD. It should be noted that it is likely that areas with increased iron ore mining and processing also have increased general industrial activity unrelated to iron. A recent review by (Cloonan et al. 2017) suggested that exposure to iron containing particles in association with genetic suggestibility through modification of IREB2 may be contributors to COPD. IREB2 is an iron regulatory protein involved in the maintenance of cellular iron metabolism. IREB2 protein expression is higher in the lung tissue samples of people with COPD. This with the addition of evidence of iron imbalance in cases of pulmonary inflammation suggests that IREB2 may play a role in the pathogenesis of COPD (DeMeo et al. 2009).

[Figure 6]

Cardiovascular Effects

There are three broad hypotheses about how exposure to PM causes cardiovascular disease:

(1) Deposition of particles in the lung provokes a low-grade alveolar inflammation with a secondary systemic inflammatory response resulting in downstream cardiovascular exacerbations in susceptible individuals with the release of prothrombotic and inflammatory cytokines into the circulation (Sun et al. 2010; Valko et al. 2007; Wu et al. 2016a; Zhu et al. 2011).
(2) Central nervous system manipulation of cardiovascular function following PM exposure via alterations in autonomic nervous system activity which can directly and indirectly alter cardiac function (Stone et al. 2017).
(3) UFPs translocating into the circulation adversely affecting the heart by initiating arrhythmias and sudden death in susceptible subjects or having a direct effect on atherosclerotic plaques in vasculature (Sun et al. 2010; Tarantini et al. 2013).

Transition metals, including iron, in dust/soil have shown significant positive correlation with endothelin-1, intercellular adhesion molecule 1 and Ox-LDL which are biomarkers of endothelial function (Wu et al. 2015; Wu et al. 2016a). Increased levels of these biomarkers have been associated with an elevated risk of atherosclerosis and cardiovascular disease. When serum ferritin levels are high under inflammatory conditions there are also hypercoagulability and fibrin changes (Pretorius and Kell 2014). Additionally, the morphology of red blood cells alters in patients with haemochromotosis and when excess unliganded iron is added which can be reversed by the addition of iron chelators (Pretorius et al. 2014; Pretorius and Kell 2014).

Effect of Particle Size

Course particles (PM_{10}), those with an aerodynamic diameter of 2.5 - 10 μm, generally derive from resuspensions of dust and soil as well as sea salts, pollens, spores and crustal material from roads, farming and mining (Pope and Dockery 2006). Coarse particles are more likely to be deposited in the bronchial airways, affecting respiratory pathophysiological changes consistent with asthma, COPD and pneumonia (Sandstrom and Forsberg 2008). Fine particles ($PM_{2.5}$), those with an aerodynamic diameter of 0.1 - 2.5 μm, primarily derive from combustion processes including diesel and petrol, coal burning, wood burning and industrial processes such as steel mills, paper mills and smelting operations (Pope and Dockery 2006) and are more likely to be deposited in the small airways and alveoli, leading to cardiovascular events and alveolar-capillary membrane dysfunction (Sandstrom and Forsberg 2008). UFPs, those with an aerodynamic diameter of <0.1 μm, are commonly created from industrial and urban environments. UFPs commonly merge to form agglomerates of particles more than 100 nm across. In addition to the altered deposition profile of larger particles, agglomerates may exhibit a range of discrete and/or synergistic toxicities related to individual chemical constituents. The high agglomeration of UFPs is due to an increase in van der Waals forces and has been shown to vary by media and pH (Bhattacharya et al. 2012). Iron containing particles have been identified in all size components with concentrations and chemical make-up dependent on source (Genga et al. 2018, Yadav et al. 2019, Yang et al. 2019).

The smaller component of iron containing PM_{10} is able to incorporate into membrane bound vesicles, however, the larger component does not. In contrast, NPs have been shown to be incorporated into epithelial cells in aggregates of up to hundreds of particles (Könczöl et al. 2011). Many papers still consider NPs and ambient UFPs separately despite their obvious toxicological cross-over. Stone et al. (2017) published a detailed literature review comparing toxicological studies involving man-made and ambient particles with a diameter <100 nm and found that UFPs and NPs appear to share common toxicological mechanisms, in particular oxidative stress and inflammation. A major variation is that iron containing NPs are often coated which will significantly alter toxicity profiles for these species with changes in surface charge, agglomeration, cellular location and membrane solubility (Liu et al. 2013).

Nano sized iron oxide particles induce an inflammatory response with significantly increased number of BALF neutrophils in rats exposed to nano Fe_2O_3 particles (Ban et al. 2012; Demokritou et al. 2010; Park et al. 2015; Srinivas et al. 2012; Sutunkova et al. 2016). Additionally, some studies have shown an increase in ROS (Guichard et al. 2012) and cytotoxicity (Bhattacharya et al. 2012) for NPs over micro particles, however, other studies have shown no difference between them (Karlsson et al. 2009).

Effect of Morphology

Particles generated for *in vitro* research by various methods vary in size, surface area and morphology from other generated particles and naturally occurring particles in particular. Fly ash particles (**Figure 7a**), are relatively uniform in spherical shape and size, which is a feature of all iron oxide particles produced by combustion methods. The spherical shape is due to the molten nature of materials at high temperatures (Li et al. 2017). However, these particles react with other chemicals in the atmosphere causing them to lose sphericity as they move away from the source (Ault et al. 2012). In contrast, mineral dusts and salts (**Figure 7b**) are irregular in shape.

[Figure 7]

Particles formed by physically abrasive methods including grinding and crushing processes generally produce particles with rough and splintery morphologies. A good example of this are the iron containing particles found in subway PM (**Figure 8**) (Moreno et al. 2015). These particles are formed by the abrasion of train brakes on railway tracks resulting in sharp, elongated particles with a rough flake-like surface which are likely to produce significantly different toxicological effects compared to the spherules produced by combustion processes.

[Figure 8]

Iron oxides in different oxidation states also have varied morphologies. Comparative studies determined that needle-like γ-Fe_2O_3 showed a higher level of toxicity compared to the equivalent spherical Fe_3O_4 NPs (**Figure 9**) (Park et al. 2015). Similarly, rod-shaped particles were significantly more cytotoxic than spherical nano or micro Fe_2O_3 particles in rat macrophage cells (Lee et al. 2014). Nanoparticles with elongated shape, such as needle or rod-shaped particles, have altered recognition by alveolar macrophages which can lead to accumulation (Braakhuis et al. 2014, Kuroda et al. 2018). Rigid, elongated fibres may also be physically trapped more readily in the lung than their spherical counterparts (Kuroda et al. 2018).

[Figure 9]

Effect of Source

Exposure to iron oxides occurs in a variety of occupations, including welding, foundry work, metal forming and manufacturing, as well as iron-ore mining and transport. Generally, workers are exposed to substantially larger doses of airborne pollutants than the general population when at work. Below, we consider PM from a range of sources known to contain high concentrations of iron.

Steel Production and Foundries

Electric arc furnaces, which are one method used to recycle iron into steel, produce between 10 and 25 kg of dust per ton of steel (Bakkar 2014). This dust contains high quantities of iron, but is contaminated with other metals including lead, chromium, cadmium and zinc (Bakkar 2014). There was a significant increase in malignant tumours of the larynx, trachea, bronchi and lungs for electric-arc furnace workers (SMR=3.35) with the highest rates attributed to those exposed for 1-5 years (SMR=4.35) (Cappelletti et al. 2016). Squamous metaplasia (benign changes to cells) and cytological atypia (atypical cells which may develop into cancerous tissue) were both significantly higher in iron

industry workers than controls (Ahmed et al. 2013). Morbidity analysis also found a significant increase in relative risk for diabetes (RR=2.24), rheumatoid arthritis (RR=6.18), non-complicated hypertension (RR=2.23) and complicated hypertension (RR=2.01) among electric-arc furnace workers (Cappelletti et al. 2016).

There are high rates of COPD among steel-workers with a calculated relative risk of developing COPD of 5.51, which when adjusted for age and smoking became 5.11 (Bala and Tabaku 2010). Iron oxide was also highly associated (OR = 9.61) with obstructive pulmonary function impairment (Ryu et al. 2013). Iron industry employees also had significantly higher rates of viral infection and yeast infection (moniliasis) compared to controls (Ahmed et al. 2013). Oxidative markers in exhaled breath condensate were elevated in workers exposed to iron oxide pigments compared to controls (Pelclova et al. 2016). Additionally, iron was associated with endogenous thrombin production, as a marker for global coagulation, having the highest regression coefficient for any of the metals analysed in this study (53.6 95% CI -16.5 to 123.7), however, this was not significant due to a large confidence interval (CI) (Tarantini et al. 2013). A separate study found a significant increase in MDA and 8-OH-dG, both of which are markers of oxidative stress, and tail moment which is a marker of DNA breakage, in exposed foundry workers (Liu et al. 2009). Both of these studies failed to focus on iron, concentrating instead on other metals despite the fact iron was the metal of highest concentration in the PM.

Fly Ash

Coal burning is a major source of iron-containing fly ash. Magnetic phases of fly ash are particularly high in iron which has been shown to be present in a wide variety of mineral phases including magnetite, hematite, maghemite, iron-silicates, ferrite spinel complexes and others (Bourliva et al. 2017). Inhalation of fly-ash particles has been associated with respiratory and cardiovascular disease (Bourliva et al. 2017).

Subway Particles

Most inhalable-sized iron containing PM on subway platforms are flakes composed of iron oxide NPs usually also associated with additional nanomaterial products from the parent material of brake and rail systems (Moreno et al. 2015) with a coating of salts or small particles of mineral matter such as carbonates, clay and quartz (Moreno et al. 2017). There is a large amount of variation between subway systems due to design, component and usage differences (Wang et al. 2016). In subway stations where the train tracks were separated from the station area by a solid wall with sliding doors there is a significant decrease in the ambient $PM_{2.5}$ (Moreno et al. 2015; Wang et al. 2016) providing a useful mechanism by which to decrease exposure.

Exposure to subway particles caused concentration dependent cytotoxicity in CHO-1 cells at concentrations ≥ 25 μg/ml but not BEAS-2B cells (Jung et al. 2012) and a 4-fold increase in intracellular ROS (Karlsson et al. 2008). Comet assay on CHO-K1 cells showed an increase in DNA breakage at all concentrations ≥ 1.6 μg/ml (Jung et al. 2012). Micronuclei frequency, an indicator of chromosomal damage, increased significantly and was inhibited by ROS scavengers (Jung et al. 2012). DNA damage caused by subway particles was almost 2 fold higher than either Fe_2O_3 or Fe_3O_4 particles alone, with an increased ability to cause oxidative stress (Karlsson et al. 2008) suggesting

morphological, surface reactivity or synergistic factors are likely involved. Exposure of human primary bronchial epithelial cells to subway PM showed an increase in IL-8 release and a concentration dependent increase in ROS which decreased with addition of either an iron chelator (desferrioxamine) or free radical scavenger (N-acetylcysteine) (Loxham et al. 2015). In a study investigating the genotoxicity of PM from various sources including wood combustion, tyre wear and street PM, subway particles were the most genotoxic tested with 4-5 fold more DNA damage (Karlsson et al. 2006).

Mining

Iron-ore deposits occur naturally in the form of iron oxides and other salts (**Table 1**). Haematite is commonly found in banded iron formations along with sedimentary deposits of silica (quartz as chert), and carbonates (Banerjee et al. 2006). Iron-ores, including haematite, frequently occur with varying proportions of impurities such as alumina, sulphur, phosphorus, titanium, vanadium, zinc, copper, chromium, nickel, arsenic, lead, tin, and cadmium.

[Table 1]

Significant increases (99% CI) were found for increased rates of lung cancer within the mining industry in Sweden (HR=1.47). This was further analysed as priori industry groups: metal mines (HR=1.46); iron/steel mills (HR=1.07 non-significant); iron foundries (HR=1.28); and blacksmith/welding (HR=1.24 non-significant) (Jung et al. 2018). Despite an overall decrease in lung cancer among all miners in a Western Australian cohort (SIR=0.91) there was a significant increase for ever underground vs never underground for lung cancer (IRR=1.81; 95%CI 1.11, 2.93) with average annual radon exposure for Australian miners lower than the permissible limit (Sodhi-Berry et al. 2017). There was also a non-significant increase for iron ore only mining vs multiple ore mining exposure for lung cancer (IRR=1.52; 95%CI 0.98, 2.59), however, these results were not compared to the general population as confounders such as employment-related variables and smoking could not be accounted for (Sodhi-Berry et al. 2017). These results are in agreement with an earlier study which found an increased lung cancer risk at two hematite mines in China (SMR=3.7; 95% CI 2.5, 5.3; N = 6444) for underground workers. This was reanalysed for those exposed pre and post ventilation improvement in the mines with a notable decrease in risk with the improvement in ventilation (pre-ventilation (SMR=4.8) and post-ventilation (SMR=2.4)), however, there was no adjusting for smoking or radon confounders in this study (Chen et al. 1990). There were significant increases over control for taconite miners exposed to low grade iron ore, with co-exposure to silica and others: mesothelioma SIR=2.4, lung cancer SIR=1.3, laryngeal cancer SIR=1.4; and stomach cancer SIR=1.4 (Allen et al. 2015). In contrast, other studies have found no increase in rates of lung cancer among hematite miners (Lawler et al. 1985).

Overall, there is no clear evidence of a causal link between exposure to airborne iron oxide particles associated with mining and disease. However, there is evidence that exposure to dust from iron ore mining may be associated with an increased risk of mortality and morbidity. While concomitant risk factors such as smoking have been shown to be associated with increased risk, both for exposed and unexposed individuals, there is no evidence that the observed health effects are primarily related to smoking; the effects appearing synergistic. It is likely that the mechanism of injury involves Fe_2O_3 in combination with other agents, in a synergistic or additive relationship.

Geogenic Dust

Geogenic dust is naturally-derived inorganic mineral PM from the desert. There have been few studies on PM from this source due to limited monitoring in these rural, arid areas. Quantity and composition of PM from mineral dusts are largely determined by the number and extent of dust-blowing events (Engelbrecht et al. 2009). Tavares et al. (2017) found ~19% of ambient PM was iron, near one of the high iron ore mining regions of Brazil, which was higher than the iron concentration from corresponding soil samples from the area. This same paper used ^{57}Fe Mössbauer spectroscopy to determine that the samples of iron found in ambient PM collected at sites >15 km from mining areas contained large quantities of hematite that can be clearly traced to a mining origin suggesting that small PM from mining sources is capable of travelling large distances from the source (Tavares et al. 2017). Aspirated geogenic dusts in mice caused immune suppression with a decrease in alanine aminotransferase, mean corpuscular volume, plaque forming cells per million spleen cells as well as small decreases in CD4+ and CD8+ cells (DeWitt et al. 2017). There was also a small increase in creatinine levels indicating low levels of nephrotoxicity (DeWitt et al. 2017).

Urban Air Pollution

Iron containing ambient PM has been associated with road dust and brake abrasion from motor vehicles (Hoogh et al. 2013). California 6-cities found a significant correlation for iron in ambient $PM_{2.5}$ in association with respiratory hospitalization in <5 year olds following a 3-day lag, however there was no corresponding association for 5-18 year olds (Ostro et al. 2009). An earlier study found iron in $PM_{2.5}$ was significantly correlated with all cause, cardiovascular and >65 years of age mortality with a three day lag (Ostro et al. 2007). Meta-analysis of previous epidemiological studies found a large amount of variation between studies (Achilleos et al. 2017). This meta-analysis found a positive correlation between iron in ambient $PM_{2.5}$ and all cause and cardiovascular mortality however, these were not significant due to a large CI.

When ambient PM was analysed for the influence of individual metals, iron was found to have a positive (non-significant) correlation with an increase in ET-1, E-selectin, ICAM-1 and VCAM-1 (Wu et al. 2016b). ET-1 is a vasoconstrictor associated with vascular dysregulation in humans. Reduction in iron in urban PM was associated with an improvement in forced vital capacity lung function (Boogaard et al. 2013) and iron from road pollution was negatively associated with FEV1 among truck drivers (Baccarelli et al. 2014). Supporting this in *in vitro* studies there was a decrease in cell viability and an increase in ROS and IL-6 production following exposure to motor brakewear particles (Puisney et al. 2018). Iron in $PM_{2.5}$ was a significant predictor of $FENO_{50}$ and JNO levels in children following exposure to ambient PM which are markers of airway inflammation and bronchial hyper-responsiveness (Pollitt et al. 2016; Rosa et al. 2014).

Printing Toner

Black toner contains carbon black and various iron oxide pigments. Both carbon black and iron oxide can be bound to polycyclic aromatic hydrocarbons (PAHs) and heavy metals (Gminski et al. 2011). Chronic inflammation and lung fibrosis have been shown in animal models following long-term inhalation exposure to toner. *In vitro* analysis of toners containing <30% iron (by weight) showed no cytotoxicity and only moderate genotoxicity which the authors attributed to PAHs (Gminski et al.

2011). However, a series of studies investigating the co-exposure of carbon black and iron oxides have found significant *in vitro* toxicity (Berg et al. 2010; Guo et al. 2009).

Welding Fumes

Welding fumes contain metals and their oxides as well as additional complex chemical species which can be volatilized including shielding gases, paints and surface coatings. The various methods of welding all have their own associated risks and hazards. Mild steel (MS) fumes are usually 80-95% iron with some manganese (1-15%) where stainless steel (SS) welding fumes commonly contain nickel (5-10%) and chromium (15-30%) in addition to iron and manganese (Antonini et al. 2004; Sørensen et al. 2007). Welding fumes have recently been reclassified as carcinogenic to humans (Group 1) by the International Agency for Research on Cancer (IARC 2017), both for the UV produced when arc-welding and for the inhalation of welding fumes (Guha et al. 2017).

The earliest investigation of welding fumes was a 1936 paper describing the chest x-rays of 16 welders which found that 9 of the 16 patients had clear nodules present to varying degrees but no serious physical effects in any of the patients. This was subsequently defined as pulmonary siderosis, a benign condition produced by inhalation of high concentrations of iron (Doig and McLaughlin 1936). Despite the assumption that siderosis has no associated adverse health effects there have been numerous cases reported of welders developing nodular interstitial fibrosis (Funahashi et al. 1988; Khalid et al. 2009; McCormick et al. 2008). Andujar et al. (2014) found an increased metal loading in fibrous regions of the lung in welders with siderophages, ferriginous bodies, fibrotic lesions and severity of fibrosis all significantly higher in welders compared to controls.

Exposure of a mouse to an occupationally relevant dose for man showed that inhalation of SS welding fumes (*in situ* generated) following chemical initiator 3-methylcholanthrene (MCA) produced a significant increase in the number of tumours per lung ($p<0.0001$) with a significant increase in lymphoid infiltrates, presence of foreign material, hyperplasia, adenoma and total lesions supporting the association between lung cancer and welding (Falcone et al. 2017; Falcone et al. 2018b). There was also a significant increase in tumour multiplicity in A/J strain mice at 78 weeks following aspiration of SS welding fumes (Zeidler-Erdely et al. 2011). MS fumes also significantly promoted lung tumour multiplicity in MCA initiated A/J mice despite a lack of chronic inflammation and no known carcinogenic metals (Falcone et al. 2018b). Additionally, when analysing individual components of welding fumes Fe_2O_3 was the greatest contributor to lung inflammation (as a metal component by weight) (Falcone et al. 2018a). The authors suggest iron may have been responsible via formation of ROS (Falcone et al. 2018b).

Mannetje et al. (2012) found in a large Europe and UK based study that adjusting for smoking and asbestos did not attenuate the odds ratio for lung cancer in relation to occupational exposure to welding fumes. An adjusted odds ratio of 1.19 was found for individuals who had been exposed to welding fumes and an OR of 1.37 for those whose occupation was welder/flame cutter with a clear relationship between years of exposure and risk. This correlates with earlier work. Steenland (2002) found an SMR of 1.46 for welders compared to the general population and three separate meta-analyses have found an increased risk ratio for the association between welding and lung cancer (RR=1.94 (Sjogren et al. 1994), RR=1.38 (Moulin 1997), RR=1.28 (Ambroise et al. 2006)). Two of these papers examined both MS and SS and found no significant increase for SS over MS.

Strong radical generation was observed following exposure to both SS and MS fumes with deferoxamine (chelating agent) and catalase both decreasing observed ROS (Leonard et al. 2010). Older samples, however, produced significantly less ROS suggesting that studies which collect fumes on filters and extract may be less informative than those which produce fumes *in situ* (Falcone et al. 2017; Leonard et al. 2010). Blood leukocytes and neutrophils were both significantly increased in humans following MS and SS welding though these were short lived, returning to base-line by 22 hours after exposure (Kauppi et al. 2015). There was a significant association between increased ferritin levels and exposure to iron in welding fumes above 1mg/m^3 with increased 8-OH-dG and 8-OGG, which are markers of oxidation, in welder's urine samples (Pesch et al. 2015) and a significant increase in very high serum ferritin levels for iron-based welders not wearing a respirator compared to those with a respirator (Casjens et al. 2014). In addition to respirator use there is also some evidence that use of high voltage welding produces fewer biological indicators of oxidative stress than regular voltage welding (Sriram et al. 2015).

Challenges of Research to Date

Variations in the synthetic procedure used to generate iron-containing particles can lead to differing surface profiles which can significantly alter potential toxicity due to variation in the rate of aggregation and changes in cell surface recognition. Additionally, there appears to be a significant variation in the toxicity of freshly produced particles compared to those collected on filters and re-extracted (Falcone et al. 2017; Leonard et al. 2010). This process changes the surface chemistry and therefore reactivity as well as the biosolubility of these particles. Often particles prepared via chemical precipitation in a laboratory are used in *in vitro* and *in vivo* studies to replicate the effect of particular components of ambient PM, often from combustion sources. It is reasonable to assume that the reactivity and therefore toxicity of these particles would be significantly different. In line with this, few studies consider the changes to the PM while in the aerosol or the potential synergistic effects that can occur when exposed to fresh natural PM compared to aged PM collected on filters or synthesized PM.

Length of exposure in studies is also important with the separation of short term and long term health effects necessary. There have been very few studies looking at long term exposure, particularly in *in vivo* models (Valavanidis et al. 2008). Wu et al. (2016a) found that associations based on exposure metrics of 2-7 day moving averages when considering PM exposure were stronger than those based on single day metrics, suggesting cumulative exposure might better capture air pollution effects than single day exposures. As was the case of for the tobacco industry, the mining and steel industries appear to have significant input into the funding of research into the toxicity of iron oxide, leading to a potential unconscious bias in the presentation of findings. All researchers should be aware of this potential bias when reviewing published work.

In industry-based epidemiological studies, controls are often taken from other parts of the same company (e.g. surface-workers). These workers have a reasonable probability of still being exposed to dusts and gases from the mines, albeit at lower concentration, or may have previously worked underground. Using a population-based control cohort of individuals who have not been exposed through employment corrects for this (Hedlund et al. 2006). Additionally, when evaluating epidemiological studies you need to consider the 'healthy-worker survivor' effect, where individuals who are susceptible to adverse health following inhalation of PM have an increased probability of

leaving the industry which results in a work force that may not be representative of the general population, thus the statistics are likely an underrepresentation of results (Sodhi-Berry et al. 2017).

Aerosol dosimetry studies, which rely heavily on a standardized model of a young healthy male with even distribution of inhaled particles throughout the lung may not be representative of real life particle deposition, particularly in individuals with reduced lung health. Deposition hot-spots can lead to poor predictions of dose in some regions of the lung, particularly the trachea-bronchial airways, with suggestions that local doses might be out by a factor of several hundred in some regions (ECETOC 2013; Phalen et al. 2010). Instillation, which is the method used in the majority of *in vivo* studies involving iron-containing PM, is not a good model for inhalation toxicology (Brown et al. 2005). Additionally, a large proportion of available toxicity data for all PM, including iron, is performed on fixed 2D cell cultures which may not provide an adequate representation of toxicity as they do not have the cell-cell and cell-matrix interactions of an *in vivo* system (Lee et al. 2009).

Lung overload is a condition where the clearance mechanisms of the lung are unable to cope with the load of PM. This condition induces an impairment in alveolar macrophage (AM) mediated pulmonary particle clearance and loss of AM motility (ECETOC 2013). Rat models are particularly sensitive to lung overload with rats chronically exposed to high concentrations of insoluble particles experiencing a reduction in pulmonary clearance; this has been shown to lead to pulmonary fibrosis and benign and malignant tumours (Brown et al. 2008; Olin 2000; Pauluhn and Wiemann 2011). Hamsters and mice have shown cases of overload where clearance is overwhelmed but the mechanisms do not appear to be the same as in rats (Olin 2000). Humans, however, are significantly less sensitive to lung overload with epidemiological studies unable to find a definitive link between exposure to poorly soluble particles of low toxicity and an increased risk of developing lung cancer (ECETOC 2013). This is likely to be caused by differences in particle retention and clearance in these species.

Differences in the anatomy of rats and humans may affect their long-term particle retention and therefore their chronic toxicity effects (Pauluhn and Wiemann 2011). In addition to complications involving overload, there are significant differences in clearance rates between rats and humans. The rat clears >80% of particles from the TB region in ~2 hours; where the same level of clearance in the human lung takes >16 hours (Brown et al. 2005). As rats clear PM significantly faster than humans, to simulate a human model, rats would need to be exposed to significantly higher concentrations and these concentrations are likely to induce overload conditions (Brown et al. 2008). As such, rats are not a good model for human inhalation toxicology. For acute exposures rats appear to be less susceptible to inflammatory responses than humans. However, for chronic exposures to high levels of PM, overload of AM clearance occurs in rats making them more susceptible to adverse pulmonary effects (Brown et al. 2005, 2008).

A decision was made at a workshop meeting in 2000 that despite the complications relating to overload, the rat was still the most useful *in vivo* model available as it is appropriate to select the most sensitive species when determining potential human risk (Olin 2000). The problem with this is that anytime high levels of inflammation or tumorigenesis are detected in a rat model following inhalation or instillation of PM, the overload condition is blamed for the toxicity observed and the results are ignored. The rat is, therefore, not a useful model for human inhalation toxicology as the

rat under overload conditions, rather than acting as a sensitive model, has become a scapegoat of toxicological outcomes.

Conclusions and Future Directions

Epidemiological studies across a range of workplaces with high levels of iron oxide exposure have shown correlation to a range of disease states including cancer, cardiovascular disease and a range of respiratory diseases. These results have not been well replicated in *in vitro* and *in vivo* models. Following inhalation of iron oxide containing PM the particles are rapidly taken up into macrophages and epithelial cells with *in vivo* studies providing evidence of translocation of iron oxide particles to numerous organs including the brain. This is particularly relevant for UFPs including commercially generated NPs. Iron is able to become biosoluble following inhalation which can generate ROS via the Fenton reaction leading to lipid, protein and DNA oxidation. In line with this there have been suggestions that anti-oxidants such as omega 3 in fish oil, may lessen the oxidative effects of PM exposure (Romieu et al. 2008). There is also evidence that decreasing systemic iron concentrations via phlebotomy can lead to a significant reduction in both primary (all-cause mortality HR=44; 95% CI 0.21, 0.92, p=0.028) and secondary (nonfatal myocardial infarction and stroke HR=0.34; 95% CI 0.19, 0.61 p <0.001) outcomes in patients ≤ 55 years of age with peripheral arterial disease (Zacharski et al. 2011).

No clear conclusions can be drawn from cytotoxicity studies involving iron oxide particles with a clear need for the use of more appropriate *in vitro* cell lines both in terms of a suitable choice based on the expected target organ as well as cell lines with appropriate levels of lysosomal activity (Kornberg et al. 2017). Additionally, the source of the particles needs to be considered in both *in vitro* and *in vivo* studies with evidence that freshly produced particles appear to produce higher toxicity than purchased particles or those collected on filters and re-extracted. In particular, care should be taken in these studies to attempt to replicate the PM surface chemistry, especially likely oxidation states of the metals, to develop a more accurate model of toxicity. It is likely that in addition to the important role of surface chemistry, particle morphology and synergistic effects, leading to potential redox cycling both in the aerosol and once incorporated into lysosomes, will have a marked effect on particle toxicity. There is a requirement to employ more appropriate animal models for *in vivo* studies, with rats not providing the ideal model due to induction of AM overload. As well as appropriate routes of exposure with evidence suggesting that instillation is not likely to produce a similar level of exposure to inhalation.

Exposure limits for iron oxide are outlined in **Table 2**. Australian and US guidelines place a limit on iron oxide fume exposure of 5 mg/m^3 (measured as iron) (Kornberg et al. 2017; Safe Work Australia 2013). These levels are substantially higher than the PM limits and are unlikely to be reached, even in workplaces with high levels of iron oxide exposure such as welding and foundry work. Moving forward there needs to be a reassessment of iron exposure, particularly in environments where high iron concentrations are likely with the consideration of exposure limits for iron-containing UFPs separately from $PM_{2.5}$.

[Table 2]

Overall the data on the toxicity of iron oxide PM by inhalation is inconclusive, however, the studies summarized in this article clearly suggest that iron may be involved in a ROS pathway leading to toxic effects following inhalation and is potentially not the innocuous, poorly soluble particle it has previously been characterized as. Our recommendations include an expansion of epidemiological, *in vivo* and *in vitro* studies, integrating the concepts outlined above, such as method of particle preparation, cell line type, and animal model, to solidify our understanding of the complex biological interactions of these particles.

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Tables

Table 1: Chemical structure, properties and sources of iron oxides (Banerjee et al. 2006; Park et al. 2014a; Teja and Koh 2009).

Chemical Formula	Name	Oxidation State	Properties	Sources/Uses
α-Fe_2O_3	Hematite, ferric oxide	Fe(III)	Highly stable; rhombohedral corundum; weakly ferromagnetic or antiferromagnetic (<260 K)	Most common form in mineral ore. Synthesized via precipitation in the liquid phase. Uses: major source of iron for steel manufacturing; pigments; jewellery, radiation shielding.
γ-Fe_2O_3	Maghemite	Fe(III)	Isometric, cubic or tetrahedral defect spinel; ferrimagnetic	Naturally occurs via weathering of magnetite, synthesized. Uses: magnetic tape (audio/video/data etc), biomedicine.
Fe_3O_4	Magnetite, ferrous-ferric oxide	Fe(II,III)	Cubic inverse spinel; ferrimagnetic (strongest of all transition metal oxides)	Naturally found in igneous, metamorphic and sedimentary rock. Most commonly mined iron ore. Uses in magnetic applications, toner, pigments, steel manufacturing, synthetic catalysts, water purification, ferrofluids.
FeO	Wüstite	Fe(II)	Fe deficient (~0.85:1) Isometric, cubic; antiferromagnetic	Rare form of iron oxide produced in highly reducing environments.

Table 2: United States workplace exposure limits for the inhalable fraction of iron oxide. OSHA – Occupational Safety and Health Administration; NIOSH – National Institute for Occupational Safety and Health; ACHIH – American Conference of Governmental Industrial Hygienists (Banerjee et al. 2006; EPA 1984; Kornberg et al. 2017).

OSHA	The legal airborne permissible limit (PEL) is 10 mg/m^3 (measured as iron) averaged over an 8 hour work shift
NIOSH	The recommended airborne exposure limit is 5 mg/m^3 (measured as iron) averaged over a 10 hour work shift
ACGIH	The recommended airborne exposure limit is 5 mg/m^3 (measured as iron) averaged over an 8 hour work shift

Figure legends

Figure 1: Airborne particles by size including thoracic coarse particles ($PM_{10-2.5}$), fine particles ($PM_{2.5}$), ultrafine ($PM_{0.1}$) and various components.

Figure 2: Flowchart describing the systematic review selection process to identify articles describing *in vivo*, *in vitro*, or epidemiological studies involving iron oxide or iron oxide containing PM via inhalation or instillation published in the past 10 years.

Figure 3: Estimated deposition of particles inhaled into the human body. Adapted from Chow and Watson (1998).

Figure 4: Fate and known or suspected effects caused by iron oxide particles following inhalation (Brook et al. 2010; Kell 2010; Kornberg et al. 2017; Kunzmann et al. 2011; Niemann et al. 2017; Stone et al. 2017; Zhu et al. 2009).

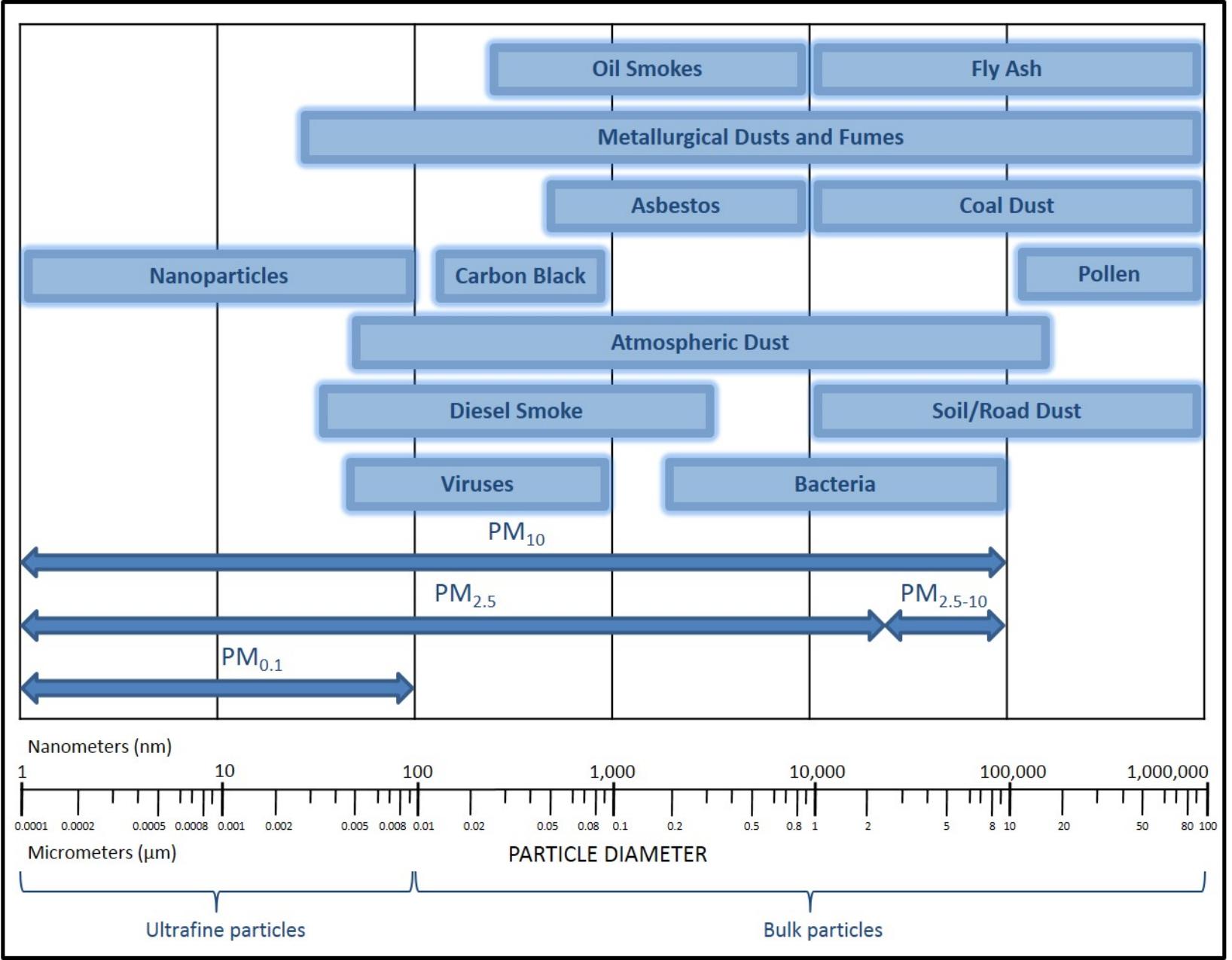
Figure 5: Equations describing the Fenton reaction leading to the generation of the hydroxyl radical and subsequent oxidation of cellular biomolecules mediated by iron. Adapted from Funke et al. (2013).

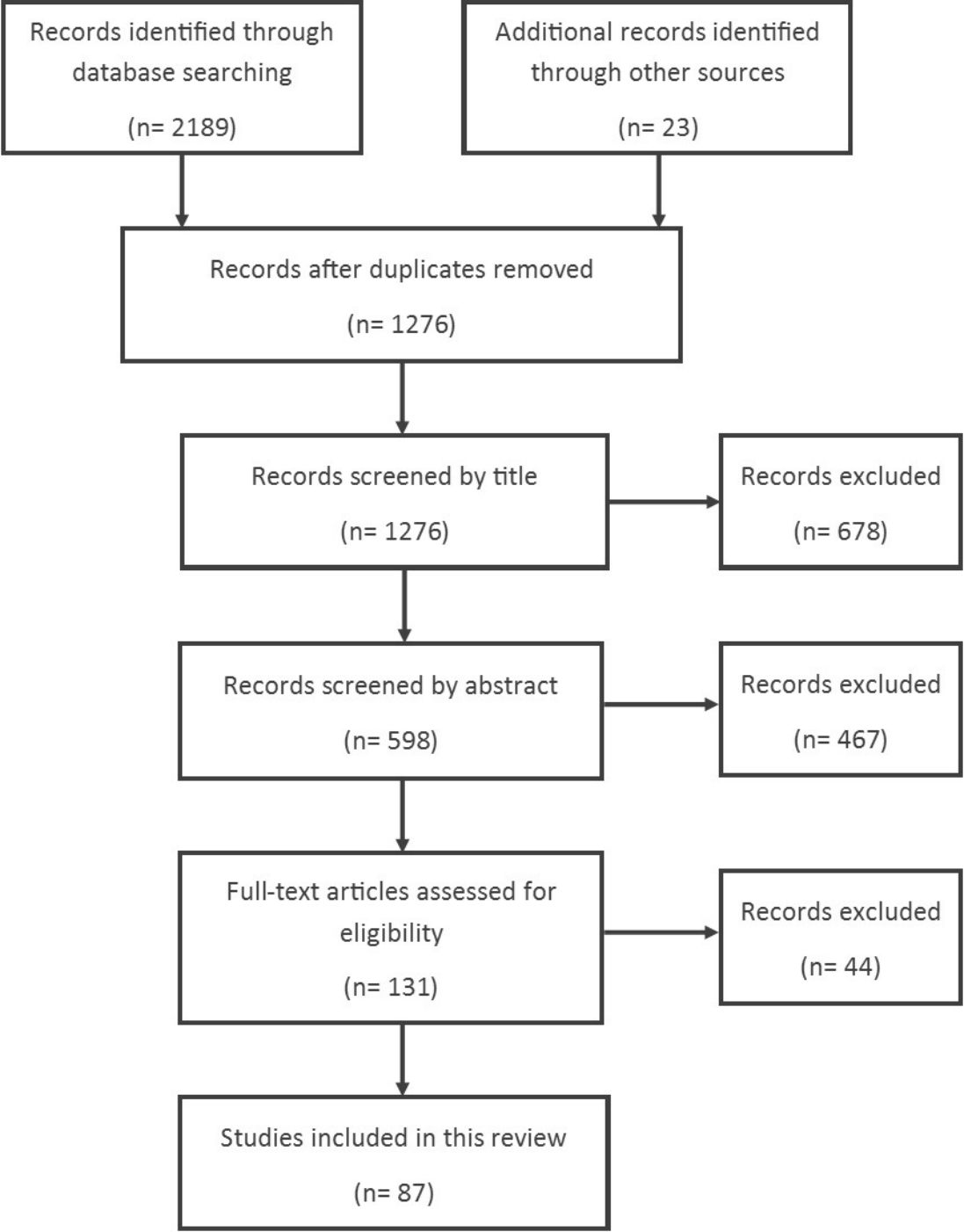
Figure 6: Comparison of workplace iron exposure and COPD mortality rates a) location of UK steel processing plants in 1986, image adapted from British Steel archive, Tata Steel and UK Steel data (PA Media 2018) b) COPD mortality rates 2008-2012, relative risk range 0.40-3.34 lightest - darkest (British Lung Foundation 2018) c) location of UK iron mines throughout history provided with permission by Gazetteer of British Collieries (not all of these mines would have been active during the lifetime of the individuals referenced in Figure 5b) (Gill 2019).

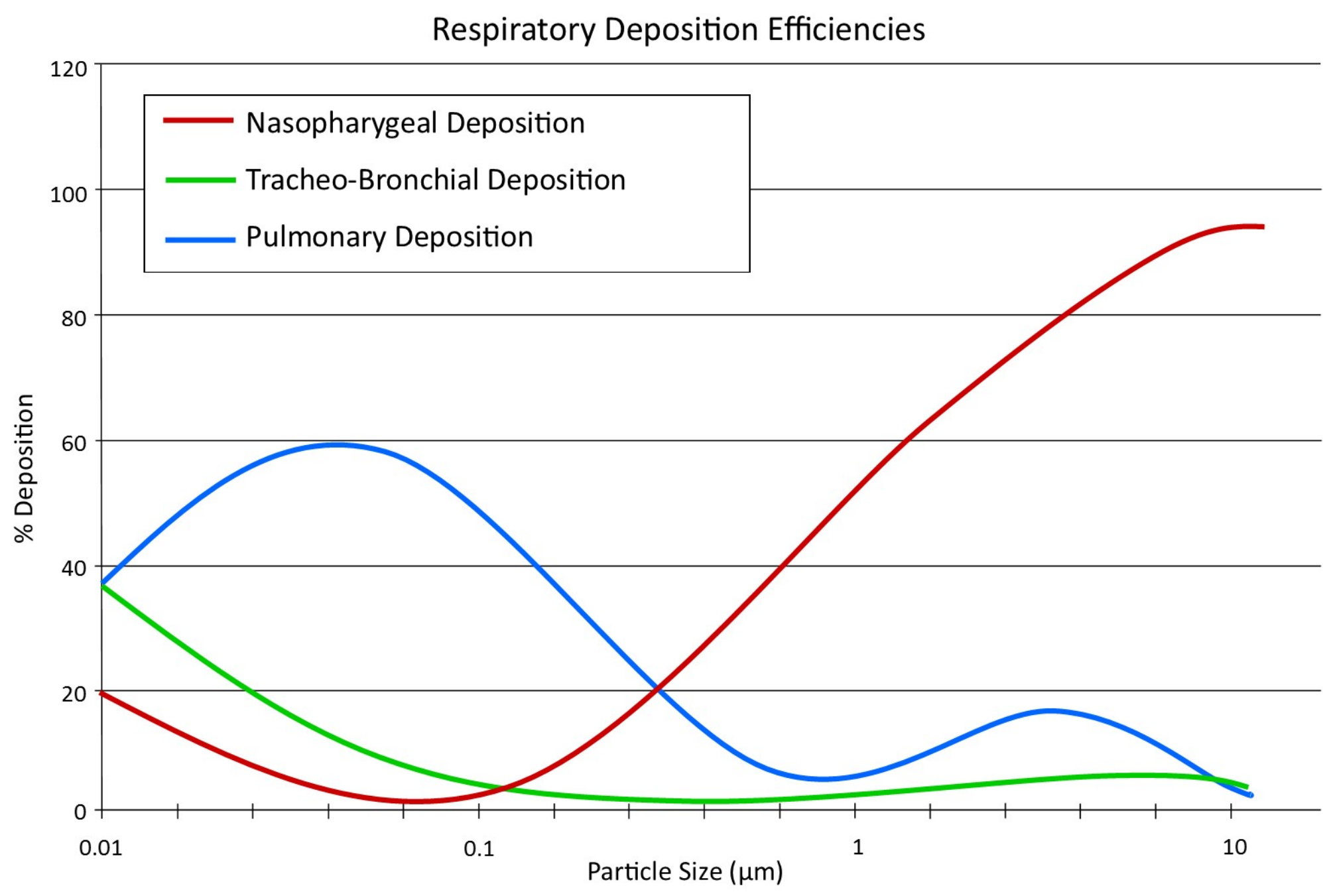
Figure 7: SEM images demonstrating morphologies of iron PM from different sources. a) fly ash particles b) mineral dust. Replicated, with permission, from Ault et al. (2012).

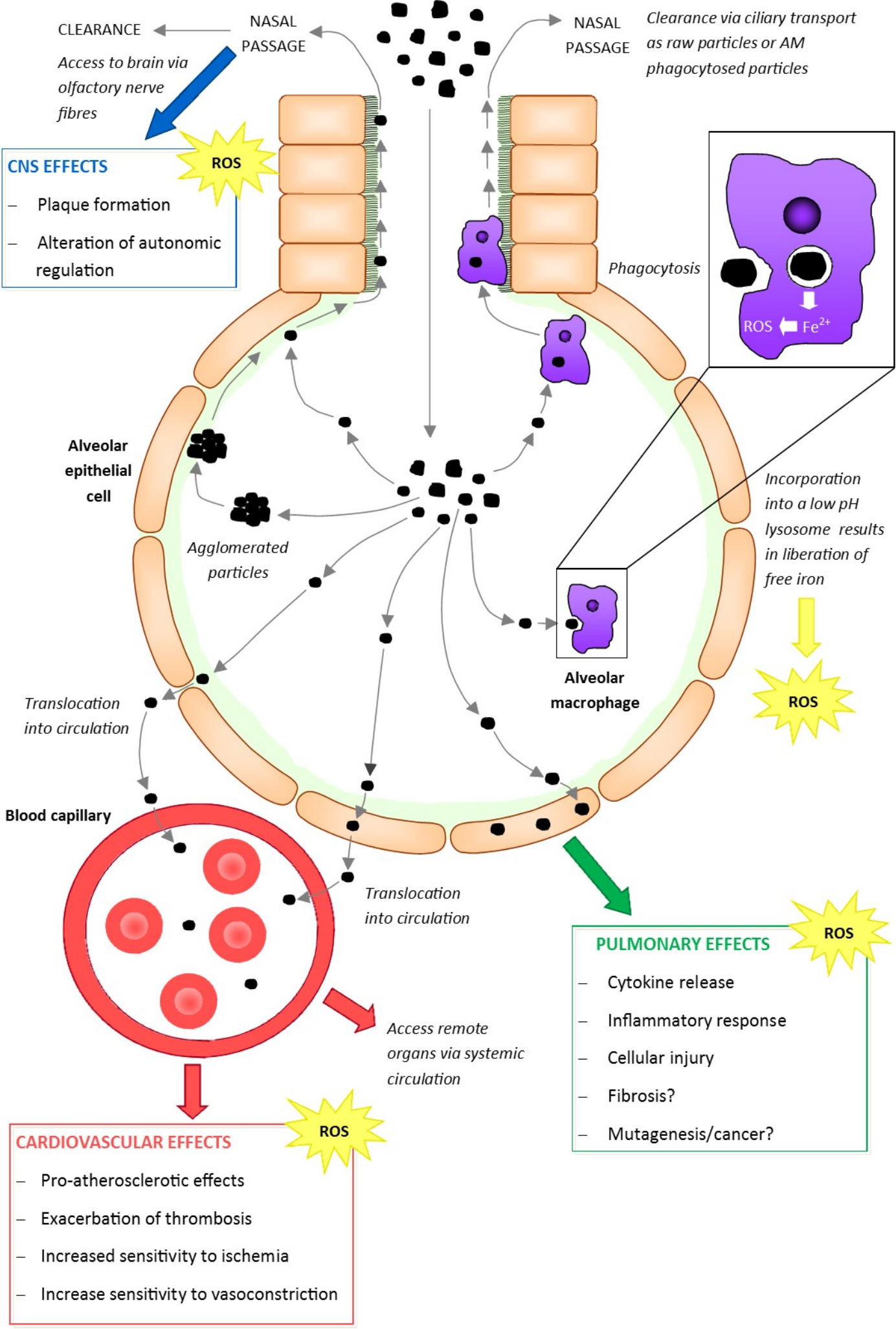
Figure 8: SEM images demonstrating the typical morphological aspect of iron PM in subway samples with flaky and splintery morphologies. Replicated, with permission, from Moreno et al. (2015).

Figure 9: TEM images showing the gradual oxidation of spherical Fe_3O_4 NPs (0 min) to form needle-like γ-Fe_2O_3 particles (60 min). Replicated, with permission, from Park et al. (2015).


Oil Smokes
Fly Ash
Metallurgical Dusts and Fumes
Asbestos
Coal Dust
Nanoparticles
Carbon Black
Pollen
Atmospheric Dust
Diesel Smoke
Soil/Road Dust
Viruses
Bacteria
PM10
PM2.5
PM2.5-10
PM0.1
Nanometers (nm)
1
10
100
1,000
10,000
100,000
1,000,000
0.0001 0.0002 0.0005 0.0008 0.001 0.002 0.005 0.008 0.01 0.02 0.05 0.08 0.1 0.2 0.5 0.8 1 2 5 8 10 20 50 80 100
Micrometers (µm)
PARTICLE DIAMETER
Ultrafine particles
Bulk particles


Records identified through database searching
(n= 2189)
Additional records identified through other sources
(n= 23)
Records after duplicates removed
(n= 1276)
Records screened by title
(n= 1276)
Records excluded
(n= 678)
Records screened by abstract
(n= 598)
Records excluded
(n= 467)
Full-text articles assessed for eligibility
(n= 131)
Records excluded
(n= 44)
Studies included in this review
(n= 87)


Respiratory Deposition Efficiencies
Nasopharygeal Deposition
Tracheo-Bronchial Deposition
Pulmonary Deposition
120
100
80
60
40
20
0
% Deposition
0.01
0.1
1
10
Particle Size (µm)


CLEARANCE
NASAL PASSAGE
Access to brain via olfactory nerve fibres
NASAL PASSAGE
Clearance via ciliary transport as raw particles or AM phagocytosed particles
ROS
CNS EFFECTS
– Plaque formation
– Alteration of autonomic regulation
Phagocytosis
ROS
Fe2+
Alveolar epithelial cell
Agglomerated particles
Incorporation into a low pH lysosome results in liberation of free iron
ROS
Alveolar macrophage
Translocation into circulation
Blood capillary
Translocation into circulation
PULMONARY EFFECTS
ROS
– Cytokine release
– Inflammatory response
– Cellular injury
– Fibrosis?
– Mutagenesis/cancer?
Access remote organs via systemic circulation
ROS
CARDIOVASCULAR EFFECTS
– Pro-atherosclerotic effects
– Exacerbation of thrombosis
– Increased sensitivity to ischemia
– Increase sensitivity to vasoconstriction

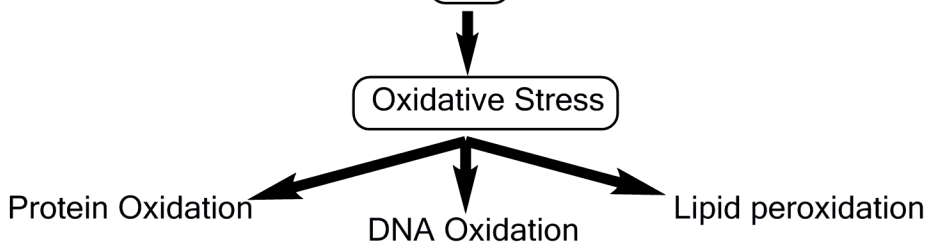
$Fe^{3+} + O_2^{-\cdot} \longrightarrow Fe^{2+} + O_2$ [1]

Fenton Reaction

$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + OH^- + OH\cdot$ [2]

Overall Haber-Weiss Reaction

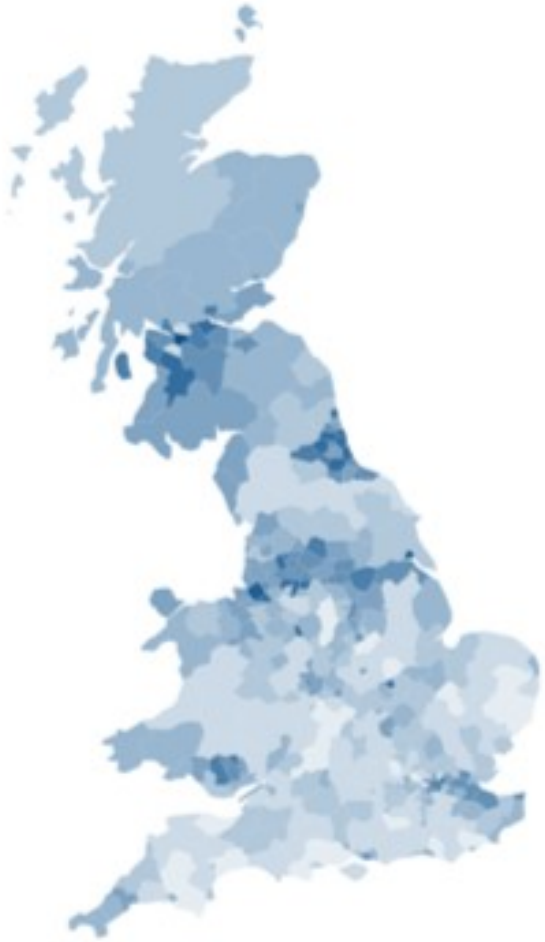
$O_2^{-\cdot} + H_2O_2 \longrightarrow O_2 + OH^- + \boxed{OH\cdot}$ [3]



(a)

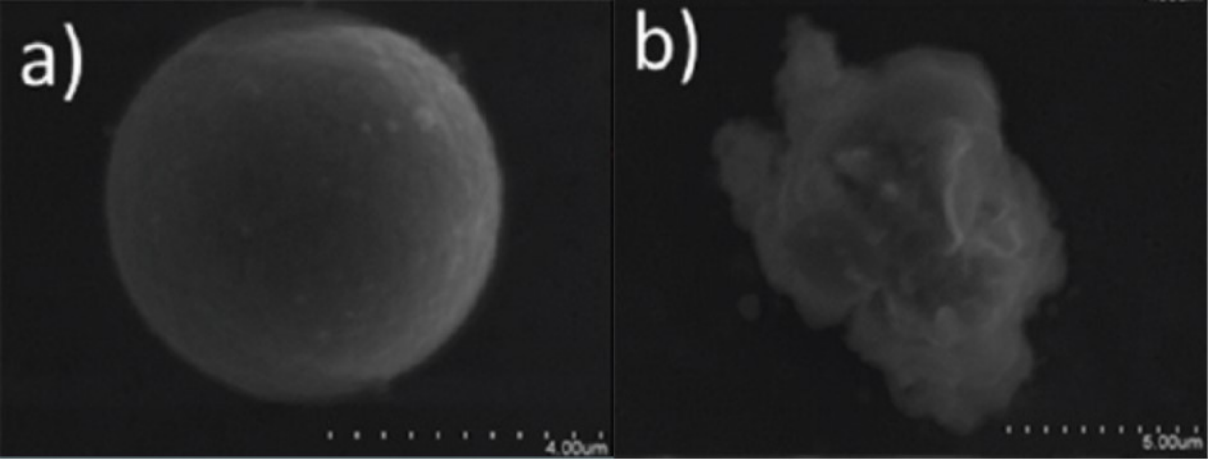

1986
39
Main steelworks owned by British Steel

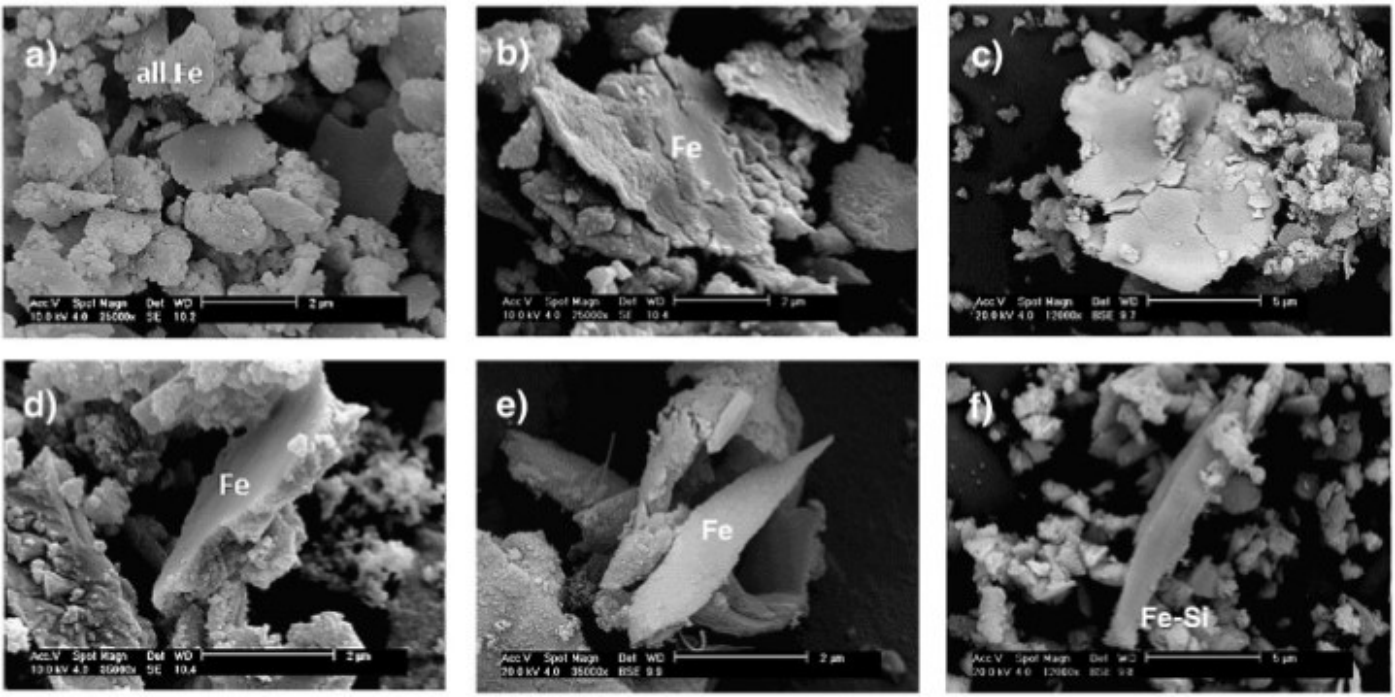
(b)

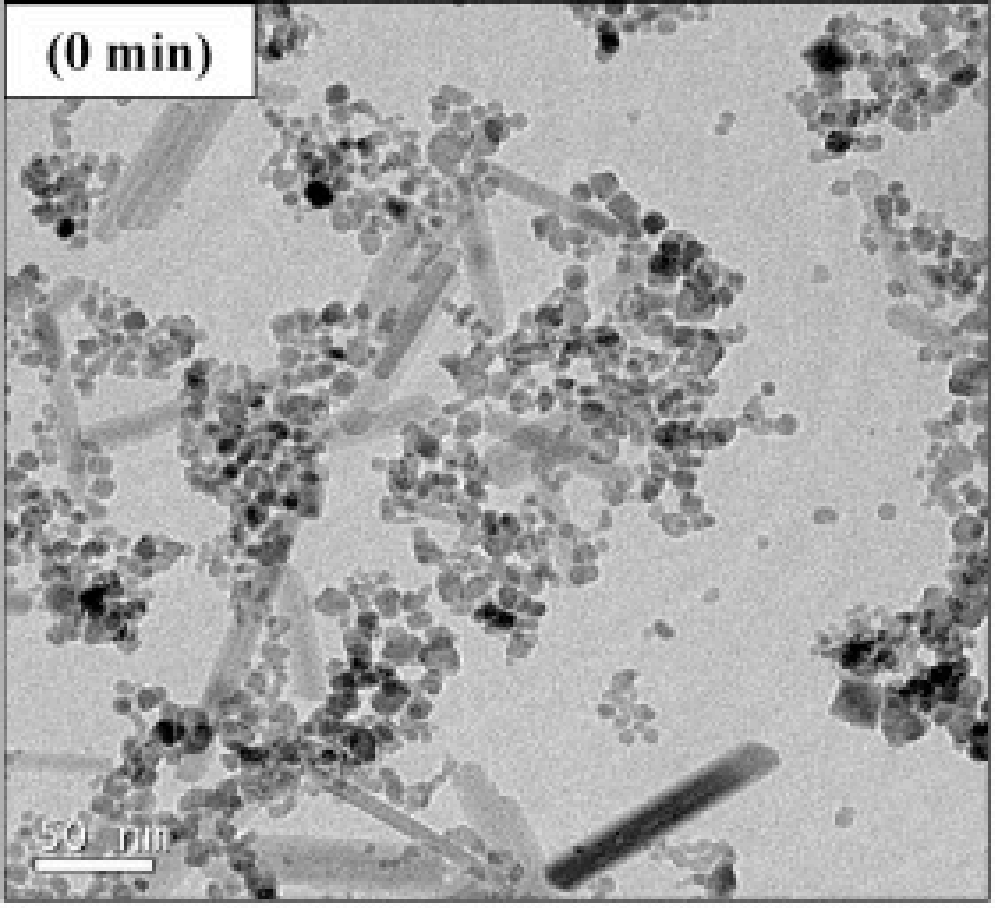


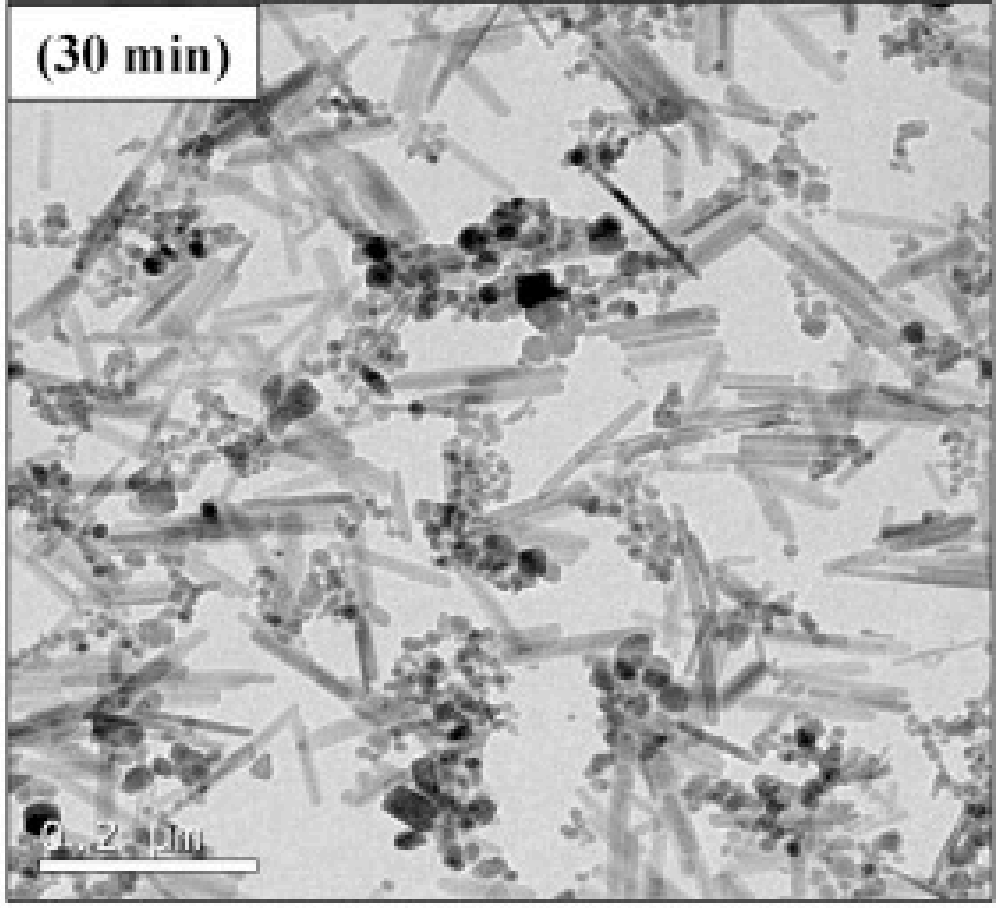
(c)

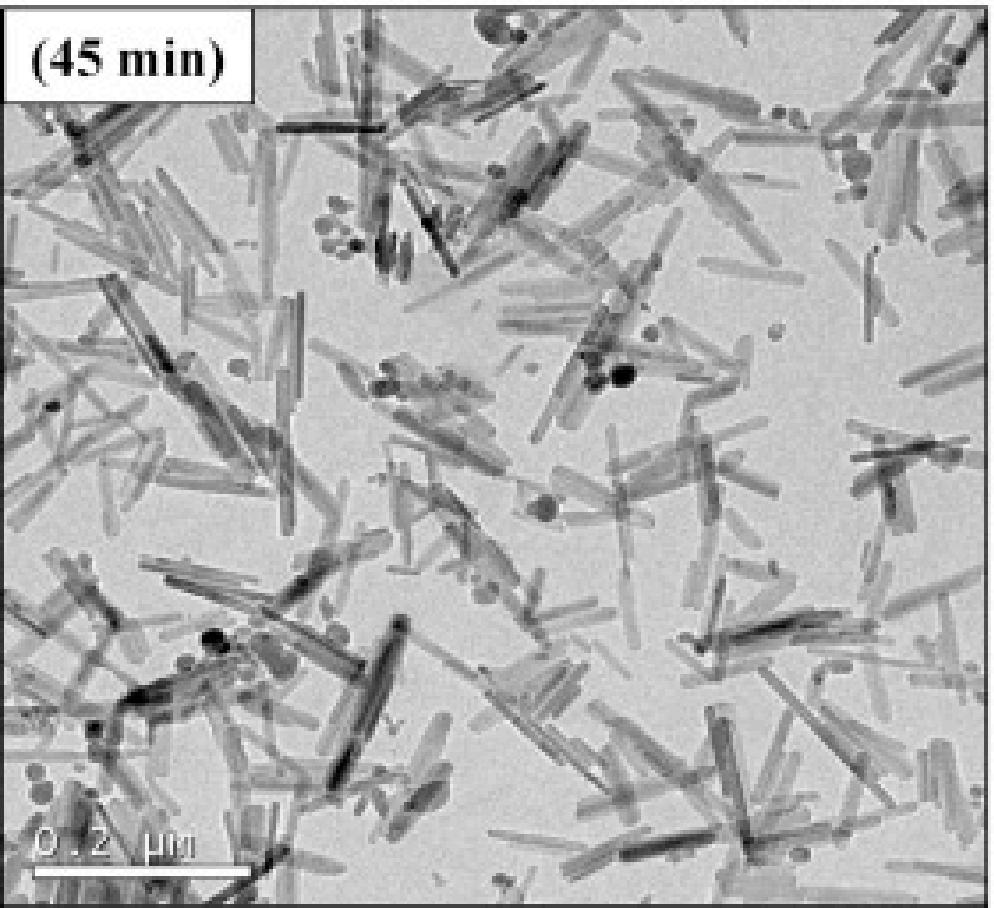

SCOTLAND
Aberdeen
Dundee
United Kingdom
NORTHERN IRELAND
Isle of Man
Dublin
Manchester
Liverpool
ENGLAND
Cambridge
Oxford
London
Brighton
Southampton

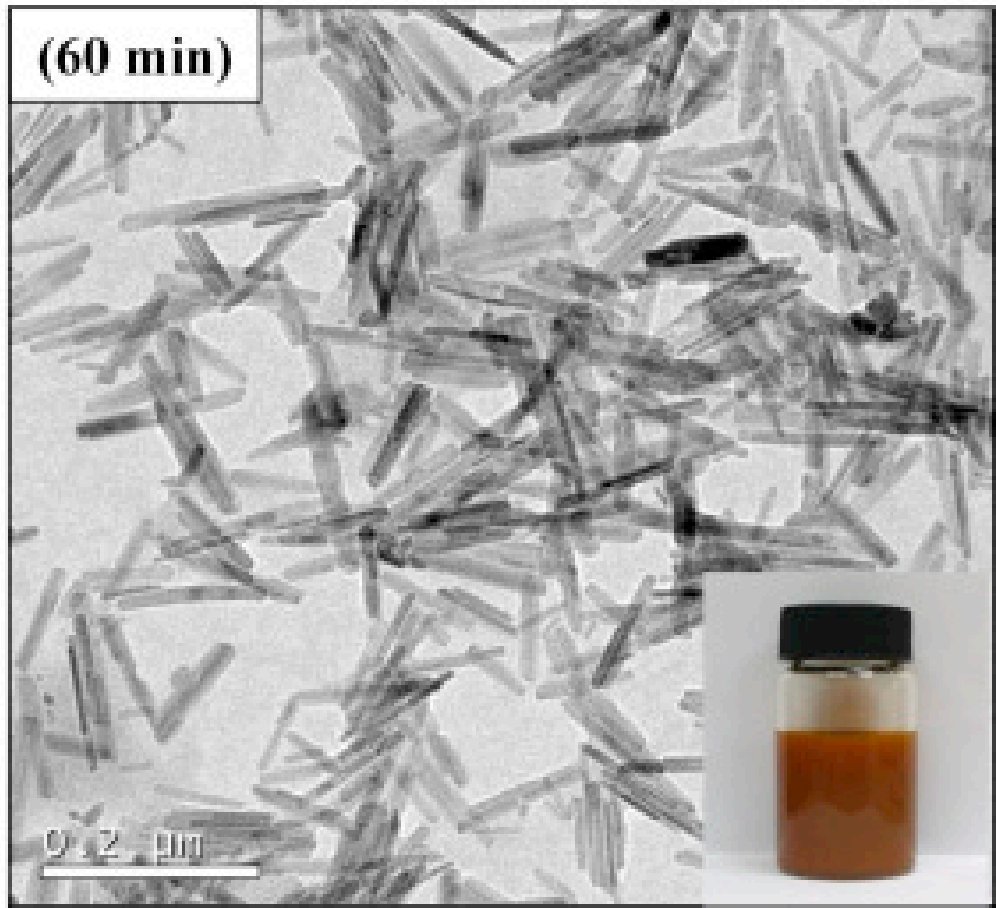

a)
4.00um
b)
5.00um


a)
all Fe
b)
Fe
c)
d)
Fe
e)
Fe
f)
Fe-Si


(0 min)
50 nm


(30 min)
0.2 μm


(45 min)
0.2 μm


(60 min)
0.2 μm